Hepatitis A Vaccine versus Immune Globulin for Postexposure Prophylaxis

John C. Victor, PhD, MPH,[1] Arnold S. Monto, MD,[1]
Tatiyana Y. Surdina, MD,[2] Saida Z. Suleimenova, MD,[3]
Gilberto Vaughan, PhD,[4] Omana V. Nainan, PhD,[4]
Michael O. Favorov, MD, PhD,[5] Harold S. Margolis, MD,[4]
Beth P. Bell, MD, MPH[4]

[1]Dept of Epidemiology, University of Michigan School of Public Health
[2]Dept of Epidemiology, Kazakhstan Ministry of Health
[3]Virology Reference Laboratory, Kazakhstan Ministry of Health
[4]Div of Viral Hepatitis, US Centers for Disease Control and Prevention
[5]Div of International Health, US Centers for Disease Control and Prevention

Immune Globulin Postexposure Efficacy among Household Contacts

Brooks, et al, 1953	88% (95% CI 16 to 98%)
Hsia, et al, 1954	92% (95% CI 42 to 99%)
Ashley, 1954	91% (95% CI 70 to 97%)
Mosley, et al, 1968	87% (95% CI 44 to 97%)
Silverberg, et al, 1970	79% (95% CI 18 to 95%)
Pavia, et al, 1990	100%

- Only Mosley and Silverberg used placebo control.
- Only Ashley and Pavia excluded secondary cases within 14 days of illness onset in index case.
- Only Pavia used diagnostic serologic tests.

Field trial of hepatitis A vaccine versus immune globulin for postexposure prophylaxis

Almaty, Kazakhstan: ~1.2 million residents

Hepatitis A occurs year round, but outbreaks involving large numbers of children occur annually in the fall and winter.

>95% of cases are hospitalized.

Primary Objective

To compare the efficacies of hepatitis A vaccine and IG in the prevention of laboratory-confirmed symptomatic hepatitis A when given within 14 days of exposure to a symptomatic index case of hepatitis A.

Study Participants

- Household or daycare contacts of index cases
- 2 to 40 years of age
- Exposed to index case within 2 weeks after index case symptom onset
- No history of hepatitis A or receipt of hepatitis A vaccine or IG (within past 6 months)
- No medical diagnosis of liver disease
- No contraindications to receipt of vaccine or IG

Interventions

- Hepatitis A vaccine (VAQTA®, Merck & Co., Inc.) at age-appropriate licensed dose for pre-exposure protection
- Immune globulin (Massachusetts Biological Laboratories) at 0.02 mL/kg
- Both interventions administered intramuscularly in the deltoid

Study Design

- 1:1 randomization *within* households or daycare center classrooms
- Participants blinded to intervention
- Study physicians administering interventions (unblinded) were different from those conducting follow-up (blinded)
- Weekly follow-up for 8 weeks postexposure

Trial Schedule

Event	Performed within 14 days of illness in index case	Time Postexposure (week)							
		(1)	(2)	3	4	5	6	7	8
Informed consent	X								
Demographic and baseline symptom data	X								
Immunization (vaccine or IG)	X								
Serologic evaluation									
total anti-HAV	X								
IgM anti-HAV	X				X				X
ALT	X				X				X
Serum PCR	X				X				X
Stool PCR*									
Phone symptom inquiry		X	X	X		X	X	X	
Week 4 questionnaire					X				
Final visit questionnaire									X

*Virus detection by PCR examined on stool samples from contacts who became ill, with collection occurring anytime during follow-up when the subject becomes ill. A special visit may have been made where blood specimens were also collected for serologic, biochemical and virologic analyses.

Primary Endpoint

1. Positive for IgM anti-HAV
2. A serum ALT level at least 2x the upper limit of normal during an episode of illness with no other obvious cause;
3. jaundice; pale stool; dark urine; abdominal pain/upper right quadrant pain; nausea; vomiting; loss of appetite; malaise; or an axillary temperature of 37.5°C or higher with no other obvious cause.

Primary Hypothesis (Noninferiority)

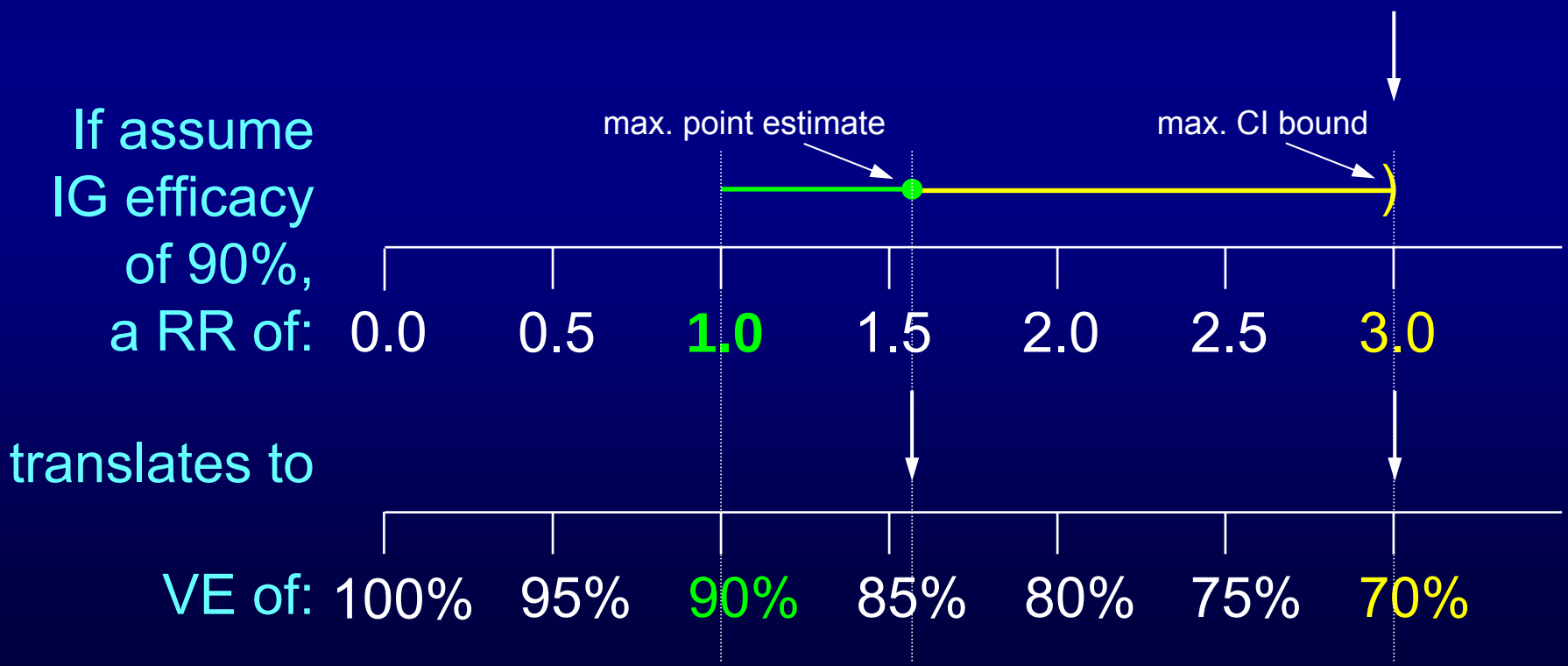
Among those initially seronegative contacts who receive each intervention within 14 days of exposure to an index case of hepatitis A, the proportions with laboratory-confirmed symptomatic hepatitis A with onset between 15 and 56 days postexposure will be similar in the two intervention groups.

Statistical Criterion for Noninferiority

Based on confidence intervals:

H_o: $P_{vaccine} / P_{IG} \geq 3.0$ (H_o: RR ≥ 3.0)

H_a: $P_{vaccine} / P_{IG} < 3.0$ (H_a: RR < 3.0)



Secondary Objectives

To compare the efficacies of hepatitis A vaccine and IG in the prevention of…

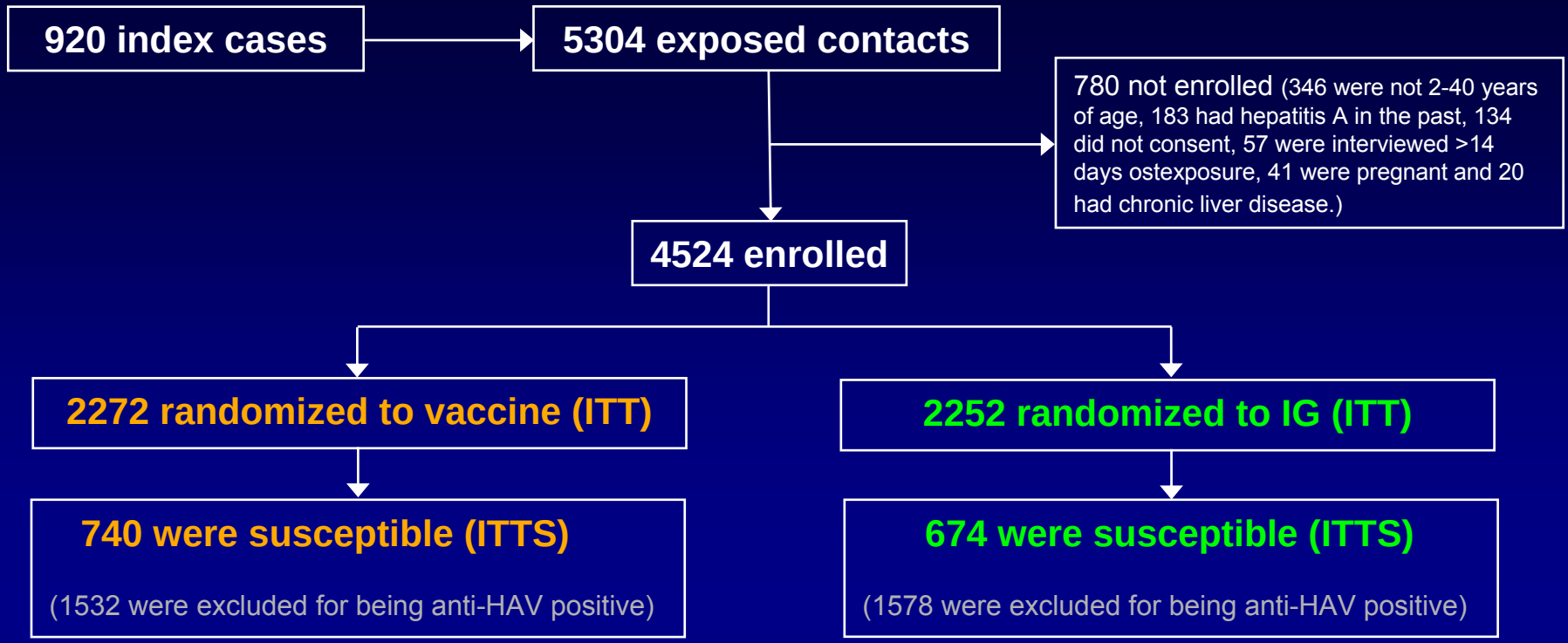
a. probable symptomatic hepatitis A
   (any symptom, IgM anti-HAV+, and ALT≥2x ULN *or* HAV RNA PCR+)

b. probable icteric hepatitis A or
   (subset of category "a" having icteric illness)

c. subclinical hepatitis A
   (asymptomatic, IgM anti-HAV+, and ALT≥2x ULN *or* HAV RNA PCR+)

when given within 14 days of exposure to an index case of hepatitis A.

Results


920 index cases
5304 exposed contacts
780 not enrolled (346 were not 2-40 years of age, 183 had hepatitis A in the past, 134 did not consent, 57 were interviewed >14 days ostexposure, 41 were pregnant and 20 had chronic liver disease.)
4524 enrolled
2272 randomized to vaccine (ITT)
2252 randomized to IG (ITT)
740 were susceptible (ITTS)
(1532 were excluded for being anti-HAV positive)
674 were susceptible (ITTS)
(1578 were excluded for being anti-HAV positive)

Characteristics of Contacts in Intent-to-Treat Susceptibles Dataset

N=1414	Vaccine n=740		IG n=674	
	Freq	**Percent**	**Freq**	**Percent**
Sex				
Female	395	53%	376	56%
Contact Type				
Household	629	85%	575	85%
Age (years) of:				
Index Case	12 ± 9		12 ± 9	
Contact	12 ± 8		13 ± 10	
Day of immunization	10 ± 3		10 ± 3	

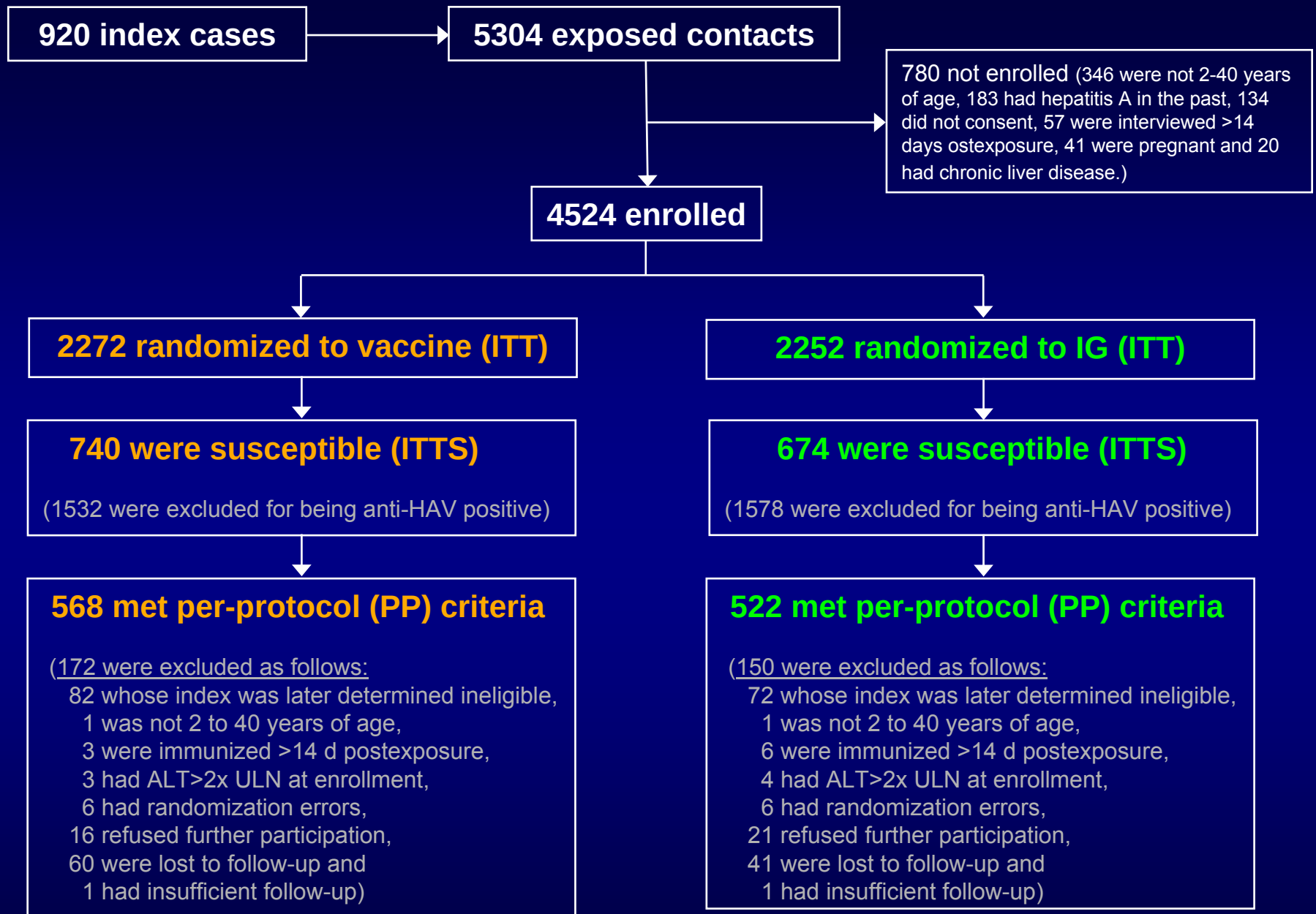
Clinical Outcomes During Follow-up

- 29 vaccine recipients had an illness confirmed by IgM anti-HAV+ and ALT elevation
  - Of these, IDMC determined that 26 were valid primary endpoints
- 22 IG recipients had an illness confirmed by IgM anti-HAV+ and ALT elevation
  - Of these IDMC determined that 18 were valid primary endpoints

Characteristics of Primary Endpoints

Characteristics of cases of hepatitis A meeting the primary case definition among contacts. n=44.

Characteristic	Vaccine (n=26) Mean	Vaccine (n=26) Range	IG (n=18) Mean	IG (n=18) Range	p-value
Time of immunization postexposure	10 ± 2 days	6 - 14 days	10 ± 2 days	6 - 12 days	0.403
Time of illness onset postexposure	25 ± 4 days	17 - 33 days	24 ± 4 days	16 - 33 days	0.560
Age of case	11 ± 9 years	2 - 34 years	17 ± 12 years	5 - 40 years	0.075
Average peak ALT leval measured at time of illness	1001 ± 397 U/L	156 - 1610 U/L	725 ± 461 U/L	66 - 1500 U/L	0.040
HAV RNA+ in serum and/or stool	62%		56%		0.761
Had icteric illness	73%		61%		0.515
Had nausea, vomiting and/or abdominal pain	85%		83%		1.000


920 index cases
5304 exposed contacts
780 not enrolled (346 were not 2-40 years of age, 183 had hepatitis A in the past, 134 did not consent, 57 were interviewed >14 days ostexposure, 41 were pregnant and 20 had chronic liver disease.)
4524 enrolled
2272 randomized to vaccine (ITT)
2252 randomized to IG (ITT)
740 were susceptible (ITTS)
(1532 were excluded for being anti-HAV positive)
674 were susceptible (ITTS)
(1578 were excluded for being anti-HAV positive)
568 met per-protocol (PP) criteria
(172 were excluded as follows:
82 whose index was later determined ineligible,
1 was not 2 to 40 years of age,
3 were immunized >14 d postexposure,
3 had ALT>2x ULN at enrollment,
6 had randomization errors,
16 refused further participation,
60 were lost to follow-up and
1 had insufficient follow-up)
522 met per-protocol (PP) criteria
(150 were excluded as follows:
72 whose index was later determined ineligible,
1 was not 2 to 40 years of age,
6 were immunized >14 d postexposure,
4 had ALT>2x ULN at enrollment,
6 had randomization errors,
21 refused further participation,
41 were lost to follow-up and
1 had insufficient follow-up)

Characteristics of Contacts in Per-Protocol Dataset

N=1090	Vaccine n=568		IG n=522	
	Freq	Percent	Freq	Percent
Sex				
Female	297	52%	289	55%
Contact Type				
Household	470	83%	437	84%
Age (years) of:				
Index Case	12 ± 9		12 ± 9	
Contact	11 ± 8		13 ± 9	
Day of immunization	10 ± 2		10 ± 2	

Risks of Developing Hepatitis A Among Vaccine and IG Recipients (PP)

	Risks		Relative Risk
	Vaccine (n=568)	IG (n=522)	
	No. (risk)	No. (risk)	RR (95% CI UB)†
Clinical endpoints:			
Primary Any symptom plus IgM Anti-HAV+ *and* ALT≥2x ULN	**25 (4.4%)**	**17 (3.3%)**	**1.35 (2.40)‡**
Secondary Any symptom plus IgM Anti-HAV+ *and* ALT≥2x ULN *or* PCR+*	29 (5.1%)	19 (3.6%)	1.40 (2.40)
Icteric illness plus IgM Anti-HAV+ *and* ALT≥2x ULN *or* PCR+	18 (3.2%)	12 (2.3%)	1.38 (2.76)
Subclinical endpoints:			
Asymptomatic plus IgM Anti-HAV+ *and* ALT≥2x ULN *or* PCR+	20 (3.5%)	16 (3.1%)	1.15 (2.12)
Clinical + Subclinical	49 (8.6%)	35 (6.7%)	1.29 (1.90)

* Includes all primary endpoints and six clinical cases which did not meet the primary endpoint criteria.
† Exact one-sided confidence intervals.
‡ Values used for calculations of implications for vaccine efficacy.
PP = per-protocol; RR = relative risk; CI UB = confidence interval upper bound

*Implications for Vaccine Efficacy Based on Assumed IG Efficacy, Observed IG Failure Rate and Calculated RR Upper Bound**

Assumed IGE	SAR	VE at point estimate of RR	VE at 95% CI UB of RR
100%	∞	100%	100%
95%	65%	93%	88%
90%	**33%**	**86%**	**76%**
85%	22%	80%	64%
80%	16%	73%	52%

*based on per-protocol analysis of the primary study endpoint

Summary

- Efficacy of hepatitis A vaccine postexposure is quite high and similar to that of IG.
- Risk of hepatitis A for vaccine recipients was never >1.5% the risk for IG recipients.
- Some evidence that IG may attenuate clinical illness.
- No evidence that vaccine given in the second week after exposure resulted in lower clinical protection.
- Household contacts experienced the highest transmission rates.

Acknowledgements